REMARKS

This paper is being filed in response to the Office Communication dated August 19, 2002 that was issued in the above-identified application. Applicants request a three-month extension of time and enclose the fee required under 37 C.F.R. §1.17(a)(3). Applicants also enclose herewith a Supplemental Information Disclosure Statement, a Form PTO-1449, copies of the 41 documents cited, and the fee required pursuant to 37 C.F.R. §1.17(p). Applicants respectfully request reconsideration of the above-identified application in light of the amendments and remarks presented in the instant Amendment.

Claims 37-52 and 57 are pending. Upon entry of the instant amendment, claims 37-57 will be cancelled and new claims 58-86 will be added. Claims 43, 45, 46, 48, and 57 have been cancelled in favor of new claims 58-62 respectively. Claims 42-48, 50-52, and 57 have been cancelled in favor of new claims 63-74 respectively. Claims 42-48, 50-52, and 57 have also been cancelled in favor of new claims 75-86 respectively. Therefore, Applicants assert that new claims 58-86 are fully supported by the specification as filed and do not constitute new matter.

As a preliminary matter, Applicants wish to point out that the Examiner has previously acknowledged that claims 43, 45, 46, 48, and 57 relate to patentable subject matter. Claims 43, 45, 46, and 48 have been cancelled in favor of new claims 58-61 respectively, which are written in independent form. Claim 57 has been cancelled in favor of new claim 62 wherein structure (XXXII) has been amended. Therefore, Applicants believe that these claims are in condition for allowance.

Claims 37-42, 44, and 49 remain rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. The Examiner has maintained the allegation that the terms

"prodrug" and "drug" are indefinite as defining function rather than structure. The Examiner further alleges that the phrase "wherein hydroxylation ... the drug moiety" in claims 38-41 is unduly functional. The Examiner also alleges that claim 49 is unduly functional. The Examiner has acknowledged that Applicants are permitted to be their own lexicographer, but has rejected claims 37-42, 44, and 49-52 as allegedly indefinite for using the term "drug" in a manner that is "repugnant to the usual meaning". See Paper 20, Office Action, August 19, 2002, page 6, line 15 *et seq*.

Applicants traverse these rejections and maintain that the terms "prodrug" and "drug" are not indefinite. However, to advance prosecution of the instant application, Applicants have replaced these terms with terms that are not limited by function. For example, claims 63-73 use the term "molecule" in place of "prodrug" and the term "chemical" in place of "drug." Applicants assert that use of these terms broadens the scope of these claims, by defining the claimed structures in function-neutral language. Claims 75-86 use the term "CYP1B1 substrate" in place of "prodrug". Applicants assert that the term "CYP1B1 substrate" is a structural limitation since it defines molecules of the invention to be those having at least one functional group which is able to fit within the three-dimensional confines of the active site of this enzyme. This term also defines the chemical properties of molecules of the invention to be those which are capable of a specific chemical interaction with the active site of CYP1B1. Applicants assert that none of these terms are used in the claims in a manner that is repugnant to their usual meaning. Finally, rejection of claims 38-41 and 49 is moot since these claims have been cancelled. Applicants, therefore, assert that the instant claims are clear and definite and respectfully request withdrawal of these rejections.

Claim 57 has been rejected under 35 U.S.C. §112, ¶2 as allegedly indefinite for lack of a double bond in the carbamate functional group. The ommission of this bond was clearly a typographical error and would be understood as such by the artisan of ordinary skill. Therefore, Applicants have redrawn Formula XXXII in new claim 62 to include the subject double bond.

Claims 37-42, 44, and 49-52 have been rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not sufficiently enabled by the specification. The Examiner has alleged that determining whether a molecule is a prodrug is a three part test that requires extensive experimentation and has a low expectation of success.

Applicants traverse this rejection and assert that new claims 63-86 are fully enabled by the specification. New claims 63-73 define the claimed molecules in function-neutral language, thereby obviating the need for extensive experimentation. New claims 74-86 recite a "CYP1B1 substrate". Applicants assert that the artisan of ordinary skill would recognize that determining whether a molecule is a CYP1B1 substrate may be readily determined using the *in vitro* cytotoxicity assay disclosed in the instant application at pages 19-20 and Table 1. Clearly, since compounds must be substrates of CYP1B1 in order to be metabolized to be more active compounds by CYP1B1-expressing cells, this assay can also be used to determine whether or not a molecule is a CYP1B1 substrate. In addition, Applicants assert that the artisan of ordinary skill would recognize that determining whether a molecule is a CYP1B1 substrate may be readily determined using one or more of the assays known in the art. *See e.g.* Murray et al., 1998, *Br. J. Cancer* **77**:1040-1044 (Supplemental IDS enclosed herewith, document 11); Burke MD et al., 1985, *Biochem Pharmacol* **34**(18):3337-3345 (EROD assay; Supplemental IDS enclosed

herewith, document 31). Therefore, new claims 63-86 are fully supported by the application as filed and Applicants respectfully request withdrawal of these rejections.

Claims 37-42, 44, and 49-52 have also been rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not sufficiently described by the specification to reasonably convey to the skilled artisan that Applicants had possession of the invention. The Examiner has alleged that the term "drug" as a chemical radical is unduly functional and does not convey possession of the invention. The Examiner has observed that possession of the invention may be shown in structural chemical formulas. The Examiner further alleges that the phrase "wherein hydroxylation ... the drug moiety" in claims 38-41 is unduly functional. The Examiner also alleges that claim 49 is unduly functional. Applicants have cancelled these claims in favor of new claims 63-86.

Applicants traverse these rejections and assert that new claims 63-86, which do not recite the term "drug", are described in the specification with sufficient structural information to convey possession of the invention. One of the advantageous features of the invention is that the structural framework defined by formula Z may be combined with a vast number of chemical moieties. The chemical moiety need only have a free amino, hydroxy or thiol group through which the chemical moiety may be linked to the structural framework. *See* page 6, lines 8-9. Therefore, the only structure needed to demonstrate possession of the invention is that of the structural framework, which Applicants have provided by, *inter alia*, formulas Y and Z. Applicants note that the rejections related to claims 38-41 and 49 are moot since these claims have been cancelled.

Claim 52 has been rejected under 35 U.S.C. §112, ¶1 as allegedly containing subject matter that was not sufficiently enabled by the specification. The Examiner has alleged

that the specification lacks enablement for the treatment of cancer generally. The Examiner has questioned whether all tumor cells possess detectable levels of expression of an enzyme having CYP1B1 activity.

Applicants traverse this rejection and assert that the specification sufficiently enables the claims as introduced herein. Claim 52 has been replaced by new claims 73, 74, 85, and 86 which relate to inhibiting tumor cell growth. Support for treatment of tumors of the breast, colon, lung, oesophagus, skin, connective tissue, lymph node, brain and testis may be found in the specification as filed, *inter alia*, at page 1, lines 17-21. Support for treatment of tumors of the stomach may be found, *inter alia*, at page 2, lines 25-28. Support for treatment of bladder tumor cells, cervical tumor cells, endometrium tumor cells, kidney tumor cells, ovarian tumor cells, intestinal tumor cells, and uterine tumor cells is found in Table 1 of the instant application showing activation of drugs by CYP1B1 in combination with Murray GI et al., 1997, *Cancer Research* **57**:3026-3031 (tumors that express CYP1B1 are disclosed; hereinafter "Murray 1997"). While a copy of Murray 1997 was previously provided (Document 1, IDS filed November 2, 2000) and considered by the Examiner on December 1, 2001 (signed copy of Applicant's Form PTO-1449 included with Paper 17, Office Action dated December 5, 2001), Applicants enclose an additional copy of Murray 1997 herewith for the Examiner's convenience. Support for treatment of cervical tumor cells, colon tumor cells, and prostate tumor cells is found in Hoang et al, 2001, *British Journal of Cancer*, 85(Suppl 1):78 (CYP1B1 is expressed in cervical tumor cells; Supplemental IDS enclosed herewith, document #3); Stanley et al, 2001, *Drug Metabolism Reviews*, 33(Suppl 1):62 (CYP1B1 is expressed in colon tumor cells; Supplemental IDS enclosed herewith, document #5); and Tang et al., 2000, *Pharmacogenetics* 10:761 (CYP1B1 is expressed in prostate tumor cells; Supplemental IDS enclosed herewith,

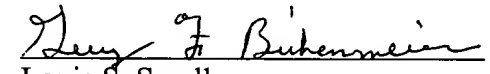
document #8), copies of which are provided herewith. Thus, claims 73, 74, 85, and 86 are fully enabled by the specification as filed and Applicants respectfully request withdrawal of this rejection.

For the foregoing reasons, Applicants believe that claims 58-86 are all in condition for allowance and respectfully request timely issuance of a Notice of Allowance.

Applicants have enclosed the fee for a three-month extension of time as required under 37 C.F.R. §1.17(a)(3), the fee for submitting new claims pursuant to 37 C.F.R. §§1.16(b) and 1.16(c), and the fee required for submitting an Information Disclosure Statement pursuant to 37 C.F.R. §1.17(p). Applicants do not believe any additional fee is required for this filing. Nevertheless, the Commissioner is hereby authorized to charge any fees required for this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Two copies of this page are enclosed.

Respectfully submitted,

February 19, 2003



Louis S. Sorell
PTO Reg. No. 32,439

Alicia A. Russo
PTO Reg. No. 46,192
Attorneys for Applicants

Guy F. Birkenmeier
PTO Reg. No. 52,622
Agent for Applicants

BAKER BOTTS, L.L.P.
30 Rockefeller Plaza
New York, NY 10112
(212) 408-2500

Enclosures